REMARKS

Reconsideration is respectfully requested in view of the following remarks.

Claims 7 – 13, all of the pending claims, stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Di Schiena (EP 0444492) in view of Saxen at al. (*Oral Surgical Oral Medical Oral Pathology Oral Radiology Endod, 1997*). This rejection is respectfully traversed.

The Examiner states that Di Schiena does not exemplify the treatment of recurrent oral aphthous ulcers, and that "*Saxen et al. teach that recurrent aphthous ulcers are a common disorder, causing pain from inflammatory sensitization of nerve endings.... Adults having aphthous ulcers were treated with 3% diclofenac in 2.5% hyaluronan, 2.5% hyaluronan or 3% viscous lidocaine. A 48% reduction in pain was observed 10 minutes after application with no significant difference between the three topical agents [see abstract]. Ulcers were smaller after treatment with HA [page 359, Table 1]*". The Examiner thus concludes that "*the skilled artisan could expect that Di Schiena's composition would be useful for the treatment of a specific inflammatory affection of the oral cavity, recurrent oral aphthous ulcers, because Saxen teaches that HA is effective for treatment of recurrent oral aphthous ulcers.*".

The Examiner, therefore, has based her reasoning on the fact that the HA was deemed to be effective against recurrent oral aphthous ulcers in view of the data stated in the abstract.

The Examiner's basis is not correct because the data making reference to the reduction of pain by 48% clearly refers ***only*** to the preparation of diclofenac/HA as clearly stated at page 359, 1st column, line 5, wherein it is stated that for diclofenac/HA a highly significant effect was observed and "*neither lidocaine nor hyaluronan were significantly different from baseline pain level*".

Therefore, the abstract of Saxen's article, if read correctly in its entirety, does not teach that HA would be useful for the treatment of recurrent oral aphthous ulcers, but that diclofenac/HA gel can be used to treat recurrent oral aphthous ulcers (RAS).

In the field of medicine, it is very difficult to understand how the Examiner can affirm that Saxen contains "effective" data for the treatment of recurrent aphtous ulcers (RAS), solely with HA, in view of the fact that RAS is a pathology of unknown origin and very difficult to treat.

In Applicant's last Response of April 20, 2010, Applicant rebutted all of the arguments of the Examiner supporting her new obviousness rejections, which are summarized as follows:

> - the use of Table II to say that HA was effective. Contrarily, in Table II at 1 hour the group receiving HA/diclofenac was significantly better, from VAS score 2.25 (baseline) to 0.798 (difference:1.452), than the group receiving only HA, from VAS score 2.89 to 2.028 (difference:0.862). Furthermore, Saxen also teaches that lidocaine at 1 hour, from VAS score 2.71 to 1.683 (difference: 1.027) was better than the group receiving only HA (from VAS score 2.89 to 2.028 (difference:0.862)). Still further, at 2 hours from the initial treatment, the group treated solely with HA gave a VAS score which was higher than at 1 hour, specifically 2.190, therefore a deteriorating situation. Thus, one of ordinary skill in the art would have known with a high degree of certainty that the treatment of ROAU was not possible.
>
> - the use of the significant pain reduction data based solely upon the use of HA. Contrarily, Saxen stated that "*A 35% to 52% pain reduction ($p<0.01$) was reported 2 to 6 hours after the application of diclofenac in hyaluronan, while hyaluronan gel alone and viscous lidocaine **FAILED** to produce significant VAS reduction*".
> - the reference to Table 1 of Saxen, when the Examiner affirmed that "*Table 1 clearly teaches that there was a reduction in lesion size. The maximum lesion size went from 9 to 6, a 30% reduction, and the smallest ulcer size went from 3 to 0.*". Contrary to the foregoing statement, Applicant demonstrated that in Table I demographic characteristics of the treatment groups are indicated and, as is well known by the person of ordinary skill in the art, the demographic characterization is carried out in a study only and solely for the purpose of guaranteeing the equivalence of the treated groups. Furthermore, the lesion size, which the Examiner referred to, (pretreatment) the p value is 0.91 and the lesion size (posttreatment) is 0.32, that means that they are not significant values in the study.

On the other hand, and this is confirmed by Saxen himself, who stated *"No significant change in ulcer diameter or clinical appearance of the ulcer was observed throughout of the trial..."*.

In the present Office Action, in the section "Response to Arguments", the Examiner does not again refer to these arguments, because she necessarily understood the correctness of Applicant's arguments and the true nature of Saxen's work.

However, she affirms that claim 7 is not inventive on the basis of only a single piece of data reported in Saxen, i.e. "*the spontaneous pain relief data of figure 2 of Saxen.*". No other data were presented by the Examiner to prove her thesis of obviousness in view of the combination of Di Schiena and Saxen.

First of all, it's hardly believable that, in the field of medicine, wherein the treatment decision is under a physician's control and responsibility, that the skilled person would have considered this kind of data in order to treat, in a significant way, a pathology like RAS.

Applicant draws the attention of the Examiner to the fact that claim 7 does not recite the treatment of pain from ulcers situated in the oral cavity, but specifically refer to the treatment of a pathology, i.e. RAS, which is pathology of an unknown origin.

Applicant reminds the Examiner, that Annex 3 attached to Applicant's response of September 28, 2008, which is a photocopy from "Oral Pathology" Third Edition, J.V Soames and J.C. Southam, Chapter 12, pages 211-227, wherein a classification of oral ulcerations is given at page 211. As stated in Table 12.1, oral ulcerations can be deemed to be divided into six (6) important classes:

1. infective: divided in its turn into the following subclasses: bacterial, viral, fungal,

2. traumatic: divided in its turn into the following subclasses: mechanical, chemical, thermal, factitious injury, radiation, eosinophilic ulcer (traumatic granuloma),

3. idiopathic: divided in its turn into the following subclasses: Recurrent aphthous stomatitis, minor aphtous ulcers, major aphthous ulcers, herpetiform ulcers,

4. Associated with systemic diseases divided in its turn into the following subclasses: haematological diseases, Gastrointestinal tract diseases, Behcet's syndrome, HIV infection, other diseases,

5. Associated with dermatological diseases: divided into the following subclasses: Lichen Planus, Chronic discoid lupus erythematosus, vescibolous diseases,

6. Neoplastic: divided into the following subclasses Squamous cells carcinoma other malignant neoplasms.

Therefore, these different classes require different treatments, and the treatment for a specific oral ulceration cannot be immediately considered relevant for other types of oral ulcerations. The reduction in pain for one of these different kinds of ulcers, does not then dictate the treatment of the diseases for which RAS ulcerations are manifested symptoms.

Specifically, from Annex I, at the time of filing the present application, as far as RAS is concerned, it was known that:

- The causes of RAS remain unknown.
- Haematinic deficiency and/or underlying systemic disease associated in a minority of patients had been observed.
- A variety of factors may operate in individual patients.

Furthermore, at page 12 of Annex 1, the last five lines thereof, it is recited "although a variety of oral ulcer may recur for example those associated with mechanical trauma and dermatological diseases, there is a group of idiopathic ulcers whose natural history is characterised by frequent recurrences over a number of years. It is to this group that the collective term recurrent aphthous stomatitis (RAS) is applied".

Therefore, it is evident that the data relating to the spontaneous pain relief is too reductive to say that it is possible to treat RAS in an effective manner, as well as its characteristic recurrence.

Furthermore, Figure 2 reports the data regarding spontaneous pain before stimulation and after stimulation of the three (3) tested groups and not the efficacy of the tested gels on RAS. Contrarily, these effects are reported in Figure 3 and in Table II, for which the Author affirms that only Diclofenac/HA group showed a **significant treatment effect,** while based upon the data where only HA was used, the data was ***not significant*** (see page 359, first column).

The foregoing conclusion is also confirmed by the chapter "Discussion" of the Saxen's article, wherein for Figure 2, Saxen **only affirmed** that for the treatment of the protective layering of the ulcer, it is important that the hyaluronan be **used as a vehicle** (see 3rd paragraph, page 360, 1st column). No therapeutic significant effects can be derived from Figure 2 of Saxen, who consequently cannot be said to teach or suggest treating RAS solely with HA. This is also confirmed by Saxen, when referring to lidocaine gel in Figure 2, for which the spontaneous pain relief was better than with HA gel, and wherein he stated that in this case **the protective layering**, like a coat on the ulcer, was made **by carboxymethylcellulose**, whose **viscosity is similar to hyaluronan** and which **shows the same properties**.

The Examiner refers to MPEP 2123 about preferred or nonpreferred embodiments and their importance in "teaching away" from the solution to say that hyaluronan is suggested as a non-preferred embodiment to treat RAS.

As shown above, this reasoning is seriously flawed and obviously incorrect, since Saxen never suggested hyaluronan as a non-preferred embodiment of different disclosed embodiments for treating RAS, but only disclosed some protective properties on the ulcers, that provide a feeling of spontaneous pain relief. This is, indeed, very far removed from teaching a therapeutic treatment of RAS, which requires not only the reduction of the pain of the ulcers, but also requires the reduction of the number of occurrences of ulcers (recurrence) and the dimensions of the ulcers in the critical occurrences. At most, Saxen teaches the use of hyaluronan as a protective layer of the ulcers with a consequent reduction in pain after stimulation of an ulcer, ***but does not teach, nor can it be said to teach, the treatment of a specific pathology.***

In the Experiment described in Annex 1, filed with the Response of September 26, 2008, Applicant achieved the following results:

(a) a statistically significant (p=0.04) reduction of ulcers on day 5 in patients treated with HA(1.65 ±0.25) if compared to the placebo group (2.4±0.26) (see table 2),

(b) a statistically significant (p=0.047), reduction on day 4 of new ulcer occurrence in patients treated with HA(2) if compared to the placebo group (10) (see table 4), and

(c) a statistically significant (P<0.001) increase of patients free from ulcers on day 7 in patients treated with HA (24) if compared with patients treated with placebo (19) see table 3.

The foregoing confirms, without any doubt whatever, that the sole active ingredient hyaluronic acid, as per claim 7, can be effectively used in the treatment of ROAU and this, most definitely, is a highly unexpected result achieved by the claimed invention, particularly in view of teaching of Saxen at al.

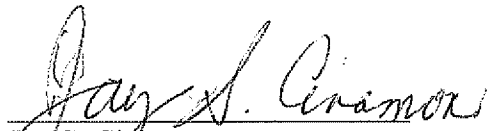
For all the above reasons, Applicant is convinced that the invention as set forth in its currently pending claims distinguishes over the prior art by a clear preponderance of the evidence. As such, the Examiner has failed to establish a case of ***prima facie*** obviousness. The rejection having been overcome, its withdrawal is respectfully solicited.

The issuance of a Notice of Allowance is solicited.

Please charge any fees which may be due and which have not been submitted herewith to our Deposit Account No. 01-0035.

Respectfully submitted,

ABELMAN, FRAYNE & SCHWAB
Attorneys for Applicant

By 
Jay S. Cinamon
Attorney for Applicant
Reg. No. 24,156

666 Third Avenue
New York, NY 10017-5621
Tel.: (212) 949-9022
Fax: (212) 949-9190